CONFIDENTIAL ID 99-31

THE UNIVERSITY OF TEXAS M.D. ANDERSON CANCER CENTER

INVENTION DISCLOSURE

In the electronic version of this form the space will expand as you type. Use the tab and/or page up/page down keys to navigate between form fields. Attach additional material as required. This form is available at www.mdacc.tmc.edu/~otd/. Refer to the Handbook of Operating Procedures, Vol. II, Section M (or call 2-7598) for assistance.

The purpose of this INVENTION DISCLOSURE is to:

- provide a complete description and documentation of an Invention
- serve as the basis for evaluation of patentability, commercial potential, and scientific merit/utility by the Office of Technology Development Technology Development
- serve as the basis for patent application(s)

Note: In order to secure a valid patent, **you must:**

1. **Disclose all persons** who made a creative contribution to the conception and/or reduction to practice of the Invention.

2. **Describe the best embodiment** of the Invention.

3. **Describe all data/information** pertaining to the Invention, whether or not it supports the Invention.

Failure to complete this form in its entirety will result in it being returned to you for completion and will delay commercialization efforts by the Office of Technology Development.

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1. a. Title of Invention: Inhibition of Superoxide Dismutase by MDA-CMP1 and Its Applications in Cancer Therapy.

b. Abstract: We discovered that a human steriod metabolite, designated as MDA-CMP1, is an inhibitor of superoxide dismutase (SOD), including the cytosolic SOD1 (CuZn-SOD) and the mitochondrial SOD2 (Mn-SOD). The inhibition of SODs by MDA-CMP1 impairs the ability of cells to eliminate peroxide radicals (O2-), a toxic cellular metabolite which is normally converted to H2O2 by SOD. We further demonstrated that treatment of cancer cells with MDA-CMP1 causes an oxidative stress in the cells and trigger apoptosis (programmed cell death) in the cancer cells, with most prominant effect observed in human leukemia cells. Importantly, no apparent cytotoxic effect was seen in normal human lymphocytes from healthy donors incubated with MDA-CMP1, suggesting that certain cancer cells (e.g. leukemia) may depend more on SOD for survival than the normal cells. Thus, inhibition of SOD by MDA-CMP1 may provide a novel approach to cancer treatment with a high therapeutic selectivity. Furthermore, because SOD is an inhibitor of erythroid progenitor cell cycling, inhibition of SOD by MDA-CMP1 may

potentially stimulate the production of red blood cells and thus alleviate the anemia associated with leukemia. The major application of this discovery is to develop MDA-CMP1 as a novel anticancer drug with the following features: (1) effective in the treatment of human leukemia with high therapeutic index. (2) useful in enhancing the effectiveness of radiotherapy and other anticancer agents, which generate free radicals in cells, for the treatment of a variety of solid tumors. (3) orally bioavailable.

c. Keyword Descriptors (max five): Steroid metabolite (MDA-CMP1); superoxide dismutase; oxidative stress; apoptosis; anticancer drug development; leukemia.

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2. Inventors' Contributions: Name each inventor, describe exactly their creative action/activity contributed to the Invention, and their percentage contribution to the Invention. **Percentage Inventive Contribution is used to calculate the inventor's share of royalties should this invention be commercialized. If an inventor was employed by an institution OTHER than MDACC at any time during their creative contribution to the invention, please note the percentage inventive contribution when at that employer.**

a. Peng Huang, M.D., Ph.D., is the principal investigator of research described in this Invention Disclosure. He initiated and directed the MDA-CMP1 research project. Dr. Huang is primarily responsible for the experimental design, analysis and interpretation of the data, and the conceptualization of the novel mechanism of action of MDA-CMP1 on superoxide dismutase and its potential clinical applications.
% Inventive Contribution: 50%

b. William Plunkett, Ph. D., is a co-investigator of the research project leading to this discovery. He actively participated in the analysis and interpretation of the experimental data and contributed to the conceptualization of the mechanism of action of MDA-CMP1 and its applications.
% Inventive Contribution: 30%

c. Li Feng, Senior Research Assistant, is responsible for performing the laboratory experiments. She also actively participated in data analysis and contributed to the technical aspects of the experimental designs.
% Inventive Contribution: 20%

d.
% Inventive Contribution:

e.
% Inventive Contribution:

f.
% Inventive Contribution:

Use additional pages if necessary.

3. a. Date the Invention was conceived (when you first thought of it or made the key observation): **: The potent anti-leukemia activity of MDA-D1 was observed; The cDNA array technology was first used to identify superoxide dismutase as the molecular target of MDA-CMP1. This constitutes the basic model for the novel mechanism of action of MDA-CMP1.**

b. Date you made the first drawing, design, formulation, construction or model, if applicable: **N/A**

c. Date of the first use of the invention, if applicable: **MDA-CMP1 was first used to induce apoptotic cell death in primary leukemia cell from a patient**

with chronic myelogenous leukemia. CONFIDENTIAL

d. M.D. Anderson Employees: Were you employed elsewhere during any part of the creation of the Invention? If so, please provide the employer's name and address, and the dates of your employment there. **No**

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4. Has/will the Invention been/be described in a meeting, poster session, seminar, published paper, or abstract (check all that apply and attach copies)?

Yes **x**____ No _____ If Yes, please provide the following information:

a. Name of Journal/Meeting: **Will be submitted for publication, journal not d cid d**

b. Date of submission: __

c. Date of Publication/Presentation (estimate if specific date unknown):

d. Date of Electronic Publication (in full or abstract) on Internet, World-Wide-Web, Gopher Site, Subscriber Service etc. (if you're not sure, contact the publisher or meeting site): **None**

e. Was the disclosure sufficient to allow someone else to duplicate the Invention?
Yes **x**____ No _____

5. **List all sources of funding** that supported the conception of the Invention and/or the Invention's reduction to practice. (Company, Institution, Various Donors Account, Government Agency, or Private Foundation, etc.)

a. Funding Source: Donors Account
Project Title: _____
Number: _____ MDA Acct No.: 8-0090095
Contract Number: _____
Contract Name: _____

b. Funding Source: _____
Project Title: _____
Number: _____ MDA Acct No.: _____
Contract Number: _____
Contract Name: _____

c. Funding Source: _____
Project Title: _____
Number: _____ MDA Acct No.: _____
Contract Number: _____
Contract Name: _____

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d. Funding Source: _____
Project Title: _____
Number: _____ MDA Acct No.: _____
Contract Number: _____
Contract Name: _____

Us additional pag s if necessary.

6. How much money has been spent to date in creating the Invention (your best estimate is ok)?
Approximately $60,000

7. Please provide names of M. D. Anderson faculty/staff (or others) whom you believe have sufficient technical knowledge in this field to serve as a scientific reviewer of your invention.

We request that this invention be kept confidential before a patent application is filed. Suggested MDA internal reviewers: Dr. Michael J. Keating and Dr. Gabriel Lopez-Berestein.

8. **Please complete 8a. through 8i. in the spaces below or on separate sheets.**

a. **What is the invention** and how could it be used? The center of this discovery is that MDA-CMP1 is found to be a selective inhibitor of superoxide dismutase and causes apoptotic death of cancer cells. MDA-CMP1 may be developed as a novel anticancer drug with the following features: (1) effective for the treatment of human leukemia with high therapeutic index, (2) useful in enhancing the effectiveness of radiotherapy and other free radicals-generating agents for the treatment of a variety of solid tumors, and (3) orally bioavailable.

b. **How does the invention work?** We demonstrated that MDA-CMP1 is a selective inhibitor of superoxide dismutase (SOD). The inhibition of SOD by this compound impairs the ability of cells to eliminate the toxic peroxide radicals (O2-), creates an oxidative stress in the cells, and triggers apoptosis (programmed cell death) in cancer cells. Our investigation further suggests that certain cancer cells (e.g. leukemia) may depend more on SOD for survival than the normal cells. Thus, inhibition of SOD by MDA-CMP1 may provide a novel approach to cancer treatment with a high therapeutic selectivity. The major application of this discovery is described above.

c. **How i th inv nuon an improvement** over the way things were done before (better results, easier to use, etc.) **or how does the Invention p rmit something c mpl tely new to b don .** Note: To be patentable, the Invention must be **"Novel"** and **"Non-obvious"** to someone like yourself.

For the first tim , we discovered that superoxide dismutase (SOD) is a molecular target of MDA-CMP1. The inhibition of SOD by MDA-CMP1 impairs the ability of cells to eliminate the toxic peroxide radicals (O2-), creates a oxidative stress, and causes the death of cancer cells. This novel discovery provides the basis for the future development of MDA-CMP1 as a new anticancer drug with important advantadgeous features including high therapeutic selectivity, potential in mechanism-based combinations with radiotherapy and other free radicals-generating agents, and oral bioavailability.

d. **Summarize the results of your in-vitro and/or in-vivo experiments** and describe to what extent the experiments have been verified.

(1) MDA-CMP1 has been shown to have potent activity against a variety of canc r cells, especially human leukemia cells (verified in vitro with cultured cells). (2) MDA-CMP1 causes no apparent cytotoxicity in normal lymphocytes (verified in vitro). (3) The key mechanism of action of MDA-CMP1 is inhibition of superoxid dismutase (verified both in vitro with purified enzyme and in whole cells). (4) Th inhibition of SOD by MDA-CMP1 creates a oxidative stress in cells, caused a loss of mitchondria membrane potential and release of cytochrome c to cytosol, which triggers the apoptosis cascade (verified). (5) We are currently evaluating th in vivo anticancer activity of MDA-CMP1 in animal models.

d. **Attach your experimental procedures and data.** You may attach a grant application, a manuscript, or poster. (See Attachments 1-18)

f. **Attach a sketch, drawing, circuit diagram, photograph, etc. if applicable. Do a prototype exist?** Yes _____ No **x**____
N/A

g. **What products and/or services could be sold** utilizing your Invention? Develop MDA-CMP1 as a new anticancer drug for the treatment of human leukemia and for combination with radiotherapy and other free radical-generating agents for the treatment of a variety of solid tumors.

h. **Attach a bibliography and enclose copies of all references** that are relevant to your Invention, including **all** relevant articles by any of the Inventors.
To our knowledge, no similar discovery has been reported in the literature.

i. **How is each reference similar to, or different from, your Invention (explain in detail)?**
N/A

9. **Do you wi h to participate in res arch** related to the commercial development and/or clinical testing of products/services arising from this Invention? Yes x No _____ . **If "no", kip th remaining items and compl te th signature page.**

10. **What ar your Clinical D v lopm nt Plans?** What are the steps that must be taken to complete the basic research and pre-clinical research (toxicology, pharmacokinetics, tissue distribution, animal efficacy, etc.)? Which steps will you perform and which steps will be done by collaborators and who are they?

(1). Evaluation of in vivo anticancer activity in animal models. This will be performed in our laboratory. It will take approximately 12 months to complete the animal experiments.
(2). Toxicology study. We plan to perform the toxicology evaluation ourselves. Collaboration with a pharmaceutical company may also be possible.
(3) Pharmacokinetics and tissue distribution will first be evaluated in animal, which will be performed mainly in our laboratory.

11. **Prepare a budget** (as you would in a grant application) with your best estimate of the time and cost (salaries, fringe benefits, materials and supplies, equipment and travel) to complet the research and get this Invention to the first phase of clinical testing.

Year 1: Evaluation of in vivo anticancer activity in animal models, approximately 12 months. Costs: Salaries for the P.I. (20%) and one research assistant (100%): $44,000. Fringe benefits: $12,320. Animals (nude mice) and maintenance: $10,000. Chemicals, equipment, and other supplies: $10,000. Travel: $1,500. Subtotal: $77,820.

Year 2: (1) Pharmacokinetics. Costs: Salaries for the P.I. (20%) and one research assistant (100%): $46,200. Fringe benefits: $12,936. Animals and maintenance: $8,000. Chemicals, equipment, and other supplies: $12,000. Travel: $1,500. (2) Toxicology study: $70,000. Subtotal: $150,636.

GMP formulation for clinical evaluation: $25,000.

Total direct costs: $253,456.

12. What companie might be intere ted in selling products or service using your Invention (provide the name, address, and phone number of a contact person at each company)?

Taiho Pharmac utical Co., Ltd. might be inter sted in supporting th pattent application of this discovery and its furth r re arch/d velopm nt. The company's address/contact person is listed below:

Taiho Pharmaceutical Co., Ltd.
1-27, Kandanishiki-cho
Chiyoda-ku
Tokyo, 101
Japan

Contact person:

Dr. Masakazu Fukushima
Dir ctor, Second Cancer Research Laboratory
Taiho Pharmaceutical Co., Ltd.
1-27, Misugidai, Hanno
Saitama, 357
Japan

T l. 0429-72-8900
Fax. 0429-72-8913

SIGNATURE PAGE

All inv ntors mu t ign thi form acknowledging that you hav r ad, und rsto d, and acc pted it a writt n, including th P rc ntage Inv ntiv Contribution (Section 2).

a.

Name: Peng Huang, M.D., Ph.D.	Department: Clinical Investigation	
Current Employer & Address (if not MDACC):		
MDACC Box #: 71	Phone #: 2-7742	Fax #: 4-4316
Home Address: 9226 Kapri Lane, Houston, TX 77025		
Social Security #: 450-73-0805		

Signature **Date**

b.

Name: William K. Plunkett, Ph.D.	Department: Clinical Investigation	
Current Employer & Address (if not MDACC):		
MDACC Box #: 71	Phone #: 2-3335	Fax #: 4-4316
Home Address: 4750 Benning, Houston, TX 77035		
Social Security #: 023-32-6056		

Signature **Date**

c.

Name: Li Feng	Department: Clinical Investigation	
Current Employer & Address (if not MDACC):		
MDACC Box #: 71	Phone #: 2-3336	Fax #: 4-4316
Home Address: 119 Lissa Lane, Sugar land, TX 77479		
Social Security #: 635-18-6743		

Li Feng

Signature **Dat**